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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MJPcb539/99PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09896	11/09/2000	10/09/1999
International Patent Classification (IPC) or national classification and IPC C12N15/54		
Applicant INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE.. et		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/04/2001	04.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09896

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-35 as originally filed

Claims, No.:

1-37 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

Sequence listing part of the description, pages:

1-20, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 2, 4-9, 18-28, 34-37
	No:	Claims	3, 10-17, 29-33
Inventive step (IS)	Yes:	Claims	1, 2, 4-9, 33
	No:	Claims	3, 10-32, 34-37
Industrial applicability (IA)	Yes:	Claims	1-34, 36, 37
	No:	Claims	35

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

II. **Priority**

The P,X documents cited in the search report (D8 and D9) are only considered relevant to the assessment of the present application, insofar as the present claims relate to Seq.ID Nos. 27-32. The rest of the subject-matter of the claims is entitled to priority from the first priority date claimed which preceeds D8 and D9.

Seq. 27 is a 1873 nt cDNA. It does not exactly correspond to any sequence in the priority documents. Presumably Fig.8a in Prio.2 (2255 nt) contains the sequence but this is not equivalent to disclosure of the discrete sequence as such. Hence, not entitled to priority.

Seq. 28 is found in Fig.3 of Prio.2. However, sequence not used in same context as in claims. Only reference to is in figure legends. This is not basis for establishing priority for claim 3 (and partially claims 4, 10-32, 34-37 insofar as these directly or indirectly refer back to 3).

Seq. 29 is not found in the priority documents.

Seq. 30 is only found in Fig.3 of Prio.2. Hence, equivalent situation as with Seq. 28. Hence, no priority rights for claim 5 and partially 10-32, 34-37.

Seq. 31 and 32 are found in Figs. 7a and 7b, respectively, of Prio.2. Hence, the exact sequences are entitled to Prio.2. However, only mention of Seq. is in figure legend so not found in same context as in claims. Hence, claim 5 and partially 10-32, 34-37 not priority-entitled.

V. **Reasoned statement on Novelty, Inventive Step and Industrial Applicability**

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- **Novelty (Art.33(2) PCT)**

D1 discloses a human EST from skeletal muscle which is 95.3% identical in a 363 bp overlap with applicants gene (Seq.ID No.3). There is a perfect match over about 165 bp and the rest of the mismatches can be attributed to sequencing errors. Importantly, the EST is recognized as being similar to rat 5'-AMP-activated protein kinase gamma chain. The chromosomal location of the EST sequence was not determined. This EST can be considered as an otherwise irrelevant disclosure (i.e. a disclosure that is not relevant to inventive step - note: the question is not whether it is the closest prior art). Hence, the disclaimers introduced by applicant in this respect are valid.

D2 and D7 have to be viewed together. D2 is effectively the continuation of the mapping started in D7. From D7, p.50, col.2 can see that in experimental family used the rn allele was found associated with the Sw120-Sw936 2-2 haplotype in 52/52 cases. This would allow selection for rn+ animals in this group. Similarly it is clear that some of markers in D2 could also provide a high diagnostic accuracy for rn+. Thus, it is arguable that such markers could be used as the basis for the assays in claims. Indeed, applicant confirms this view in that he lists the VIL1 primers of Table 2 (D2) as useable primers in claim 33. Hence, D2 anticipates **claims 29-33** (note specific mutation cited in claim 30 is intrinsic property of mutant RN. It is noted that the fact that one of applicants pairs of primers is not novel raises the question as to the source of the other primers in e.g. claim 33. This may be addressed in the regional phase.

D3 discloses an AMP-activated protein kinase. The sequence of the gamma subunit has 65% identity to Seq.ID No.1 in 917 nt overlap, 66% identity to Seq. 2 in 294 aa, 65% to Seq. 3 in 982 nt overlap. Can be considered to anticipate **claims 13 and 14** due to the lack of clarity of these claims. Argumentation regarding presence of flanking genomic sequences is disregarded since these are (i) optional and (ii) can be considered present in prior art (i.e. DNA comprising), plus (iii) parts of gene "flank" internal fragments of gene.

D4 (Seq. ID No.7) provides a gamma subunit of AMPK: 62% identity in 984 nt overlap, 65% identity in 299 aa overlap. Same relevance as D3.

D5 is simply an EST sequence of no known function or chromosomal location.

The EST has 80.5 % identity to Seq.ID No.3 over 432 nt overlap. Also, highly similar to Seq.ID No.1. Perfect matches of around 30 consecutive nt found. The sequence is an accidental disclosure and needs to be disclaimed. At present, without the disclaimer, claims **11, 13, 14, 16 and 17** lack novelty over D5

D6 is simply an EST sequence of no known function or chromosomal location. Has 93.2 % identity in 488 bp overlap to Seq.ID No.3, for example. Since this is a cloned EST, need to disclaim in **claims 16 and 17**. Disclaimer also missing from claim **13**. Hence, these claims presently lack novelty.

D8 is only relevant to the assessment to the claims insofar as these are not entitled to Prio.1. D8 discloses the human AMPK gamma 3 sequence, which is expressed in skeletal muscle. The protein has a sequence of 492 aa and includes 25aa of additional N-terminal sequence and due to a frame-shift 6 different aa in place of the 3 found by applicant. No mention of relevance to pigs. Sequence is in total 85% identical to Seq.ID No. 28. Hence, falls within non-priority-entitled **claim 3** and anticipates said claim plus claims **10-17** insofar as these refer back to 3. Since D8 can also be cited against the inventive step of these product claims, a disclaimer is not considered admissible. Probably it would be advisable to limit claims to matter entitled to Prio.1.

D9 discloses the 464 aa sequences of human and pig G3 proteins. Attention is drawn to the related DNA sequences AF214520 (pig) and AF214519 (human) which are considered incorporated by reference into D9. Hence Seq.ID Nos. 27-30 are considered disclosed by D9. The relationship between pig PRKAG3 mutation R200Q (= R41Q in application) and RN phenotype is disclosed. Since exact sequences of D9 found in Prio.2 of application, no novelty problem arises from D9.

- **Inventive Step (Art.33(3) PCT)**

Taking D3 as closest prior art for all claims (irrespective of priority), D3 demonstrates motivation to isolate AMPKs. However, given that many sequences having AMPK similarity were present at time of invention, there is no clear reason to combine D3 with any particular one of these sequences (as the sequence of

D1). Further, applicant has demonstrated highly relevant properties of his AMPK subunit which could not be expected from any particular prior art document. Thus, inventive step can be acknowledged for those claims which are formally novel and are not referred to below (i.e. in consideration of inventivity based on D8 or D9).

D8 provides sequence 85% identical to Seq.28 and 98.7% identical to Seq. 30. Sequences having very high similarity to the sequence of D8 are not inventive over D8 disclosure, insofar as these are claims for which the exact sequences of D8 have been cited against novelty (i.e. claims 3 and 10-17). Basically, disclaimer of the exact sequences would not establish inventive activity for the "surroundiing" sequences.

D9 renders present claims non-inventive insofar as relate to matter relating to Seq. ID No.28 and 30 extending beyond the exact sequences themselves (i.e. claims 3 and in part 10-32, 34-37). Given that sequences 99% (e.g.) identical to these sequences are obvious and also obvious in context of RN mutation since RN relates RN to PRKAG3, these claims are not inventive over D9 alone.

- **Industrial Applicability (Art.33(4) PCT)**

For the assessment of the present claims 35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VIII. Certain observations

- **Clarity (Art.6 PCT)**

Claim 6 - polypeptide has no function and is merely defined as having one undefined mutation in a particular area. This is a totally inadequate technical definition of a polypeptide.
Claim 10 - no specification of length remaining or of function. Definition inadequate.

Claim 13 - length of portion not specified - could be single nucleotide

Claim 14 - length of specific fragment ? / define stringent conditions in claim

Claim 15 - primer can be virtually anything as defined by reference to sequences which may have significant areas of undefined sequence.

Claims 18, 19 - in certain countries is will be necessary to specify that the transgenic animals are non-human.

Further, there are too many independent claims incl. for example 3 independent claims: 11, 13, 14 for nucleic acids (this is if one doesnt add primer claims thereto).

It is further noted that the sequence numbering on Fig page 3/8 is incorrect (2 x 240-260 !)

Translation

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 3484 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/09896	International filing date (*day/month/year*) 14 December 1999 (14.12.99)	Priority date (*day/month/year*) 23 December 1998 (23.12.98)
International Patent Classification (IPC) or national classification and IPC C09J 4/00		
Applicant HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21 July 2000 (21.07.00)	25 April 2001 (25.04.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/09896

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☒ the international application as originally filed.

☐ the description, pages 1-14, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-9, filed with the letter of 09 January 2001 (09.01.2001),
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6-9	YES
	Claims	1-5	NO
Inventive step (IS)	Claims	6-9	YES
	Claims	1-5	NO
Industrial applicability (IA)	Claims	6-9	YES
	Claims	1-5	NO

2. Citations and explanations

1. Reference is made to the following documents:
D2: DE-A-22 61 261 (cited by the applicant in the present description)
D3: JP-A-62 241 983 (see Chemical Abstracts AN 108:95873).

2. The subject matter of Claims 1-5 is not novel (PCT Article 33(2)).
Claims 1-5 relate to "activator solutions for the accelerated curing of cyanoacrylate adhesives". The intended use can only achieve a contribution to the definition of the claimed subject matter in material claims in exceptional cases. Therefore, in the absence of an indication of the effect, Claim 1 should be worded as "Solution of an organic compound which contains the structural feature -N=C-S-S-".
Compounds of this type are known, however, from D3 and are therefore not novel.
On condition that Claims 1-5 are drafted as use claims, the subject matter of these claims could be recognised as novel (PCT Article 33(2)).

3. The subject matter of Claims 6-9 is novel and inventive (PCT Article 33(2) and (3)).

3a. Claim 6: the closest prior art is D2, which describes a process that involves the use of cyanoacrylate adhesive for adhering substrates and is characterised in that it comprises an activator which contains a -N=C-S- group. The distinguishing feature between D2 and the present application is the -N=C-S-S- structural element in the activators of the process of the present application.
Consequently, the process for adhering substrates according to Claim 6 is novel.
The problem addressed by the distinguishing feature consists in the provision of novel activator substances with low volatility in a process for adhering substrates using cyanoacrylate adhesives.
The solution consists in the use of the present activators according to the distinguishing feature defined above.
This solution is considered to be inventive since (I) it could not be derived from the closest prior art that activators comprising a -N=C-S-S- structural element would result in a considerable acceleration of cyanoacrylate curing when compared with the closest prior art and (II) since this technical effect is proved in the present application.

3b. Claims 7-9: since independent Claim 6 is both novel and inventive, the process Claims 7-9, which are dependent on Claim 6, are likewise novel and inventive.